REMARKS

I. The Rejection Under 35 U.S.C. § 112, Second Paragraph Should be Withdrawn

Claims 84, 85, 87-92 and 94-109 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. In particular, the Examiner stated that it is unclear to exclude peptide species from the claimed subject matter when these peptide species do not fall within the scope of the genus of substrates that is positively recited in the claim.

The peptides of SEQ ID NOS: 19-21, 26-28, 31-33 and 35-39 are not encompassed by the genus of peptide substrates (P_2 is N, P_1 is Y, L or F, $P_{1'}$ is E, A or D and $P_{2'}$ is V) positively recited in claim 84. Therefore these sequences are deleted by amendment from the exclusion paragraph of claim 84 by the foregoing amendment.

In view of the foregoing amendment, the rejection is moot and d should be withdrawn.

II. Double Patenting

Claims 84, 85, 87-92 and 94-109 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of the claims of co-pending U.S. Patent Application No. 10/801,509. In response, submitted herewith is a terminal disclaimer to overcome this double patenting rejection. The double patenting rejection may be withdrawn in view of the terminal disclaimer.

Claims 84, 85, 87-92, 94-109 were also provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of the claims of co-pending U.S. Patent Application No. 11/753,331. Subsequent to the mailing of the present office action, Applicants elected claims to peptide substrates rather than methods of assaying for activity as examined in the present application. According to the Patent Office, the claims directed to compositions comprising peptides of the invention and methods of assaying activity are distinct (see Office Action dated January 25, 2006). Therefore, in view of the election in the Application No. 11/753,331, the provisional double patenting rejection is now moot.

In addition, the Examiner requested that the Applicants provide an appendix of the pending claims in the cited application. Attached hereto is a chart of all copending related application and the currently pending claims from U.S. Patent Nos. 10/801,509 and 11/753,331.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully submit that each of claims 84-85, 87-92 and 94-109 is in condition for allowance. Favorable examination and allowance of these claims is respectfully requested at the earliest possible date. The Examiner is invited to contact the undersigned at the number provided with any questions.

The fees for the petition for a three-month extension of time and the terminal disclaimer are submitted herewith by authorization to charge our credit card. However, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 13-2855, under Order No. 29915/00281FUS.

Dated: January 8, 2010

Respectfully submitted,

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APPENDIX A
RELATED PENDING U.S. PATENTS AND APPLICATIONS

Serial Number	Filing Date	Examiner	Elected Subject Matter
7,205,120 (09/908,943)	July 17, 2001	J. Lundgren	Methods for assaying modulators of β-secretase activity using substrates having the formula P_2, P_1, P_1', $P^{2'}$ comprise S, Y, E and V
10/801,509	March 16, 2004	J. Lundgren	Methods for assaying modulators of β-secretase activity using substrates having the formula P_2 is N, P_1 is Y, L, or F, P_1' is E, $P^{2'}$ is V
10/801,938	March 16, 2004	J. Lundgren	Methods for assaying modulators of β-secretase activity using substrates having the formula P_2, P_1, P_1', $P^{2'}$ comprise N, F, A and A
10/801,493	March 16, 2004	J. Lundgren	Methods for assaying modulators of β-secretase activity using substrates having the formula P_2, P_1, P_1', $P^{2'}$ comprise N, F, E and A
11/713,091	March 1, 2007	J. Lundgren	Peptides having the formula P_2, P_1, P_1', $P^{2'}$ comprise N, Y, E and V
11/753,331	May 24, 2007	J. Lundgren	Peptides having the formula P_2, P_1, P_1', $P^{2'}$ comprise S, Y, E and V

APPENDIX B
PENDING CLAIMS OF U.S. APPLICATION NO. 10/801,509

84. A method for assaying for modulators of β-secretase activity, comprising:

(a) contacting a polypeptide with β-secretase APP processing activity with a substrate, both in the presence and in the absence of a putative modulator compound;

wherein said substrate comprises a peptide having an amino acid sequence of at least 6 amino acids, said amino acid sequence including four amino acids defined by formula P_2P_1-$P_{1'}P_{2'}$, wherein:

P_2 is N;

P_1 comprises an amino acid selected from the group consisting of Y, L and F;

$P_{1'}$ is E;

$P_{2'}$ is V;

wherein the substrate is cleaved between P_1 and $P_{1'}$ by a human aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3 (Hu-Asp2); and

wherein said peptide does not comprise the corresponding P_2P_1-$P_{1'}P_{2'}$ portion of amino acid sequence depicted in SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, or SEQ ID NO: 39;

(b) measuring cleavage of the substrate peptide in the presence and in the absence of the putative modulator compound; and

(c) identifying modulators of β-secretase activity from a difference in substrate cleavage in the presence versus in the absence of the putative modulator compound, wherein a modulator that is a β-secretase antagonist reduces such cleavage and a modulator that is a β- secretase agonist increases such cleavage.

85. The method of claim 84,

wherein said substrate comprises a peptide having an amino acid sequence of at least 6 amino acids, said amino acid sequence including five amino acids defined by formula P_2P_1-$P_1'P_2'P_3$ and

wherein $P_{3'}$ comprises an amino acid selected from the group consisting of E, G, F, H, cysteic acid and S.

87. The method of claim 85, wherein $P_{3'}$ is E.

88. The method of claim 85, wherein the peptide comprises a sequence of amino acids defined by the formula $P_3P_2P_1$-$P_1'P_2'P_{3'}$, wherein P_3 is an amino acid selected from the group consisting of A, V, I, S, H, Y, T and F.

89. The method of claim 88, wherein P_3 comprises an amino acid selected from the group consisting of I or V.

90. The method of claim 88, wherein the peptide comprises a sequence of amino acids defined by the formula $P_4P_3P_2P_1$-$P_1'P_2'P_{3'}$ wherein P_4 is an amino acid selected from the group consisting of E, G, I, D, T, cysteic acid and S.

91. The method of claim 90, wherein the peptide comprises a sequence of amino acids defined by the formula $P_4P_3P_2P_1$-$P_1'P_2'P_3'P_{4'}$ wherein $P_{4'}$ is an amino acid selected from the group consisting of F, W, G, A, H, P, G, N, S, and E.

92. The method of claim 84, wherein the amino acids at positions P_2, P_1, $P_{1'}$, $P_{2'}$ comprise N, F, E and V, respectively.

94. The method of claim 84, wherein said substrate comprises an amyloid precursor protein (APP) amino acid sequence with a modified β-secretase processing site defined by said formula P_2P_1-$P_1'P_{2'}$.

95. The method of any one of claims 84-85, 87 or 88-92 wherein said peptide comprises an amino acid sequence having up to 50 amino acids.

96. The method of any one of claims, 84-85, 87 or 88-92 wherein the peptide further comprises a first label.

97. The method of claim 96 wherein the peptide further comprises a second label.

98. The method of any one of claims 84-85, 87 or 88-92 wherein the peptide further comprises a detectable label and a quenching moiety, wherein cleavage of the peptide between P_1 and $P_{1'}$ separates the quenching moiety from the label to permit detection of the label.

99. The method of claim 85, wherein said cysteic acid comprises a covalently attached label.

100. The method of any one of claims 84-85, 87 or 88-92 wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP β-secretase cleavage sequence: SEVKMDAEFR (SEQ ID NO: 20).

101. The method of any one of claims 84-85, 87 or 88-92 wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP Swedish KM→NL mutation, β-secretase cleavage sequence SEVNLDAEFR (SEQ ID NO: 19).

102. The method of any one of claims 84-85, 87 or 88-92 wherein the polypeptide with β-secretase APP processing activity comprises an amino acid sequence selected from the group consisting of

(a) the amino acid sequence of SEQ ID NO: 2,

(b) a fragment of the amino acid sequence of SEQ ID NO: 2 that retains β-secretase APP processing activity, wherein said fragment includes the aspartyl protease active site tripeptides DTG and DSG,

(c) an amino acid sequence that is at least 95% identical to (a) or (b), wherein the polypeptide includes the aspartyl protease active site tripeptides DTG and DSG and exhibits β-secretase APP processing activity;

(d) the amino acid sequence SEQ ID NO: 4,

(e) a fragment of the amino acid sequence of SEQ ID NO: 4 that retains β-secretase APP processing activity, wherein said fragment includes the aspartyl protease active site tripeptides DTG and DSG, and

(f) an amino acid sequence that is at least 95% identical to (d) or (e), wherein said fragment includes the aspartyl protease active site tripeptides DTG and DSG and exhibits β-secretase APP processing activity.

103. The method of any one of claims 84-85, 87 or 88-92 wherein the polypeptide with β-secretase APP processing activity comprises an amino acid sequence selected from the group consisting of

(a) the amino acid sequence of SEQ ID NO: 2; and

(b) a fragment of the amino acid sequence of SEQ ID NO: 2 that retains β-secretase APP processing activity, wherein said fragment includes the aspartyl protease active site tripeptides DTG and DSG.

104. A method according to claim 103, wherein the polypeptide with β-secretase APP processing activity comprises a polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide.

105. A method according to claim 95,

wherein the substrate is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the substrate,

wherein the cell expresses the polypeptide with β-secretase APP processing activity;

wherein the contacting comprises growing the cell in the presence and absence of the test agent, and

wherein the measuring step comprises measuring APP processing activity of the cell.

106. A method according to claim 105, wherein the contacting comprises administering the test agent to a transgenic non-human mammal that comprises the cell.

107. A method according to claim 84, wherein the polypeptide is encoded by a polynucleotide comprising the nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO; 3,

(b) a nucleotide sequence that hybridizes under the following stringent hybridization conditions to the complement of SEQ ID NO: 1 or 3:

(1) hybridization at 42°C in a hybridization buffer comprising 6x SSC and 0.1% SDS, and

(2) washing at 65°C in a wash solution comprising 1x SSC and 0.1% SDS;

wherein said nucleotide sequence encodes a polypeptide that exhibits β-secretase APP processing activity.

109. A method according to claim 108, wherein the substrate comprises a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 133, SEQ ID NO: 134 and SEQ ID NO: 5.

110. The method of claim 88, wherein the peptide comprises a sequence of amino acids defined by the formula $P_3P_2P_1$-$P_{1'}P_{2'}P_{3'}$, wherein P_3 is V, P_2 is N, P_1 is F, $P_{1'}$ is E, $P_{2'}$ is V and $P_{3'}$ is E.

APPENDIX C
PENDING CLAIMS OF U.S. APPLICATION NO. 11/753,331

21. An isolated peptide comprising a sequence of at least four amino acids defined by formula P_2P_1-$P_{1'}P_{2'}$, wherein:

P_2 comprises an amino acid selected from the group consisting of N, S, and D;

P_1 comprises an amino acid selected from the group consisting of Y, L, and Nle;

$P_{1'}$ comprises an amino acid selected from the group consisting of E, A, and D;

$P_{2'}$ comprises an amino acid selected from the group consisting of A and V; and

wherein a human Aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3 (Hu-Asp2) cleaves said peptide between P_1 and $P_{1'}$;

with the proviso that if P1'P2' comprise the sequence DA, P2P1 do not comprise the sequences NL or NNle.

23. An isolated peptide according to claim 21, wherein the Hu-Asp2 cleaves the peptide at a rate greater than the Hu-Asp2 cleaves a corresponding peptide having the P2P1 P1'P2' amino acid sequence KMDA.

27. A polypeptide comprising a peptide sequence according to claim 21, and further comprising a transmembrane domain to localize the polypeptide to a cellular membrane when the polypeptide is expressed in a eukaryotic cell.

73. An isolated peptide comprising a sequence of at least 10 amino acids having the sequence SEISY-EVEFR (SEQ ID NO:152).